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Should Corticosteroids Be Used to Treat Biopsy-Proven Drug-Induced Acute Interstitial Nephritis?: PRO

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Acute interstitial nephritis (AIN) is an underrecognized cause of AKI and occurs in 13%–20% of biopsies performed for AKI (1,2). Drug-induced acute interstitial nephritis (DI-AIN) accounts for 70% of these (2). Although numerous drugs are implicated, proton pump inhibitors (PPIs), antibiotics, and nonsteroidal anti-inflammatory drugs are common culprits, especially in the elderly. Immune checkpoint inhibitors (ICIs) have recently emerged as an important cause. AIN frequently presents insidiously as a subacute rise in serum creatinine with minimal symptoms or urinary abnormalities (3,4). Histopathologic confirmation is often necessary and may result in diagnostic delays (5). DI-AIN has a variable prognosis, with 30% developing dialysis-requiring AKI and 40%–60% progressing to CKD (2). Notably, 2% of all CKD is attributed to AIN (6,7).

DI-AIN is characterized by a type B idiosyncratic cell-mediated immunologic response triggered by the culprit drug, resulting in renal tubulointerstitial injury (8). Histology shows interstitial edema and a cellular infiltrate with predominance of CD4+ T lymphocytes, plasma cells, and eosinophils (9). The drug acts as an allergen or lowers immune tolerance (*e.g.*, ICIs). With ongoing drug exposure, acute cytokine-mediated renal injury can rapidly progress to irreversible tubulointerstitial fibrosis (TIF), noted as early as 7–10 days after initial insult, and ultimately, this results in CKD (10,11).

Immediate discontinuation of the offending drug is the first step in management of DI-AIN. Glucocorticoid therapy is frequently utilized if there is lack of renal improvement despite drug withdrawal; however, its use is controversial. Data from randomized, controlled trials (RCTs) are unavailable, and treatment guidelines are not standardized. Several case series and small retrospective studies have demonstrated benefit of steroid therapy in DI-AIN (6,10,12–15), whereas others have not (16,17). In this article, we aim to provide a rationale for why glucocorticoid therapy should be strongly considered for treatment of DI-AIN.

Glucocorticoids block cytokine production *via* several mechanisms, including inhibition of a key proinflammatory transcription factor NF-κB (Figure 1), which has a pivotal role in promoting renal inflammation in various diseases, including AIN (18,19). Within days after the onset of tubulointerstitial inflammation, there is activation of profibrotic processes *via* cytokine-mediated fibroblast stimulation and epithelial-mesenchymal transformation. This results in interstitial collagen deposition, irreversible tubular atrophy, and interstitial fibrosis (8). Glucocorticoids suppress cytokine-mediated tubulointerstitial inflammation in AIN, and if initiated early in the disease course, they may prevent TIF by attenuating the initial proinflammatory pathways (Figure 1).

Data supporting early glucocorticoid use were first provided by González *et al.* (10) in a multicenter, retrospective study of 61 cases of biopsy proven DI-AIN (the majority were antibiotic or nonsteroidal anti-inflammatory drugs induced). At 18 months, the glucocorticoid group (52 of 61 patients) had a lower serum creatinine (2.1 versus 3.7 mg/dl), more complete renal recovery, and lower dialysis dependency (4% versus 44%) compared with controls. No significant steroid adverse effects were noted with a treatment duration of 8–12 weeks. A delay in steroid initiation (13 versus 34 days) was associated with poor renal recovery. Compared with the initial renal biopsy, there was evidence of markedly less cellular infiltrate and more TIF on repeat biopsies in three patients who received delayed steroid treatment. This study suggested that prompt initiation of glucocorticoids (within 7 days) in patients with DI-AIN may improve the extent and rate of renal recovery and lower TIF and risk of future CKD. Raza *et al.* (12) demonstrated greater improvement in serum creatinine (3.4-fold versus 2.1-fold; $P=0.05$) in the steroid group (37 of 49 patients) as well as less likelihood of needing dialysis, but the latter did not reach statistical significance ($P=0.06$). Muriithi *et al.* (6) evaluated renal outcomes at 6 months post-biopsy in 83 patients with DI-AIN treated with steroids (versus 12 controls). Although there was no difference in outcomes at 6 months (likely because of the small size of the control group), the steroid group achieved 49% complete renal recovery and 39% partial renal recovery, despite

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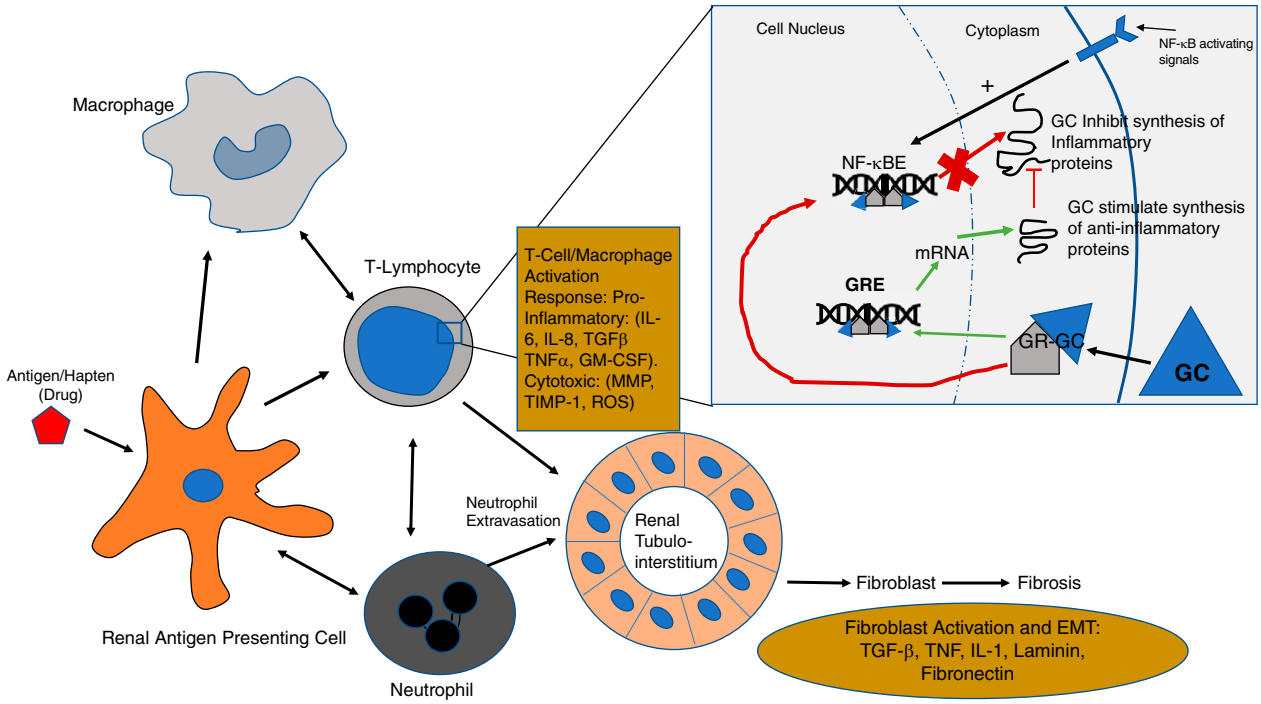

Figure 1. | Proposed mechanism of the effect of glucocorticoids (GCs) on T lymphocytes in treatment of drug-induced acute interstitial nephritis. The drug acts as an antigen and induces a delayed type 4 hypersensitivity response with activation of T lymphocytes and other immune cells. This results in a cascade of cytokine-mediated renal tubulointerstitial inflammation, which ultimately results in activation of fibroblasts, leading to tissue fibrosis and irreversible renal damage. GCs can prevent activation of inflammatory pathways *via* their effects on genomic transcription of proteins as illustrated. GCs bind to their respective cytoplasmic receptors (GRs). The GR-GC complex can bind to the glucocorticoid response element (GRE) within the T lymphocyte DNA, resulting in the upregulation of mRNA transcription and translation of anti-inflammatory proteins (shown with the green arrow). The GR-GC complex can also bind to the NF-κB element (NF-κBE), which results in inhibition of mRNA and inflammatory protein synthesis (shown with the red arrows). EMT, epithelial mesenchymal transformation; MMP, matrix metalloproteinase; ROS, reactive oxygen species; TIMP-1, tissue inhibitor of metalloproteinases 1.

having lower baseline eGFRs and more severe AKI. Longer drug exposure and a delay in initiating glucocorticoid therapy (8 versus 11 versus 35 days for complete, partial, and no renal recovery, respectively; $P=0.05$) correlated with suboptimal renal recovery. Prendecki *et al.* (13) evaluated the effect of steroids in a large retrospective study with a 2 year follow-up of patients with AIN ($N=187$; 158 of 187 were treated with steroids, and 48 of those had DI-AIN). Despite a lower eGFR in the steroid group compared with the nonsteroid group at the time of biopsy (17 versus 38 ml/min), the steroid group exhibited greater improvement in eGFR at 6, 12, and 24 months (median eGFR of 43 versus 24 ml/min at 24 months; $P=0.01$), with fewer patients progressing to ESKD (5% versus 24%; $P=0.002$). Notably, those with DI-AIN had a worse eGFR at the time of biopsy but a higher eGFR at all time points post-biopsy, demonstrating a better steroid response in those with DI-AIN compared with nondrug etiologies. Fernandez-Juarez *et al.* (14) recently published a large retrospective, multicenter study evaluating severe biopsy-proven DI-AIN ($N=182$; 19% requiring dialysis) in patients who received at least 2 weeks of corticosteroids (average dose of 0.8 ± 0.2 mg/kg per day) followed by a 9-week taper. At 6 months, the mean recovered eGFR was 34 ± 26 ml/min, with 41% achieving complete renal recovery, 46% achieving partial renal recovery, and 13% achieving no renal recovery. Delayed initiation of steroids (>29 days) correlated with poor renal recovery at 6 months. This study confirms previous findings suggesting the importance of early steroid therapy in DI-AIN. Furthermore, 74% of patients initiated on KRT in this study recovered renal function, demonstrating a beneficial role of steroids in severe dialysis-requiring DI-AIN. Duration of steroid treatment did not independently affect renal recovery, and no additional benefit was seen with treatment with high-dose steroids for >3 weeks or total treatment duration of >8 weeks. This study provides some guidance on the appropriate duration of steroid treatment. Huang *et al.* (15) recently conducted a retrospective analysis of 72 patients with severe DI-AIN requiring dialysis at diagnosis. At 6 months, 59 of 72 recovered renal function, whereas 13 of 72 progressed to CKD (eGFR <60 ml/min). A longer interval to treatment with corticosteroids was an independent risk factor for progression to CKD (odds ratio, 1.18; 95% confidence interval, 1.04 to 1.35; $P=0.01$), and a delay >22.5 days had the best predictive value for progression to CKD. This study again demonstrates that severe DI-AIN can have improved renal outcomes with timely initiation of steroids. Given the irreversibility of established TIF, several of these studies have noted poor renal recovery despite steroids in patients with higher degrees of fibrosis (6,10).

In contrast to these findings, other retrospective studies have found a lack of benefit of glucocorticoids in DI-AIN

(16,17). There are several potential explanations for these results. (*1*) Selection bias in these retrospective studies would generally favor outcomes in those not treated with steroids, as steroids would be trialed in patients who fail to improve with drug discontinuation. Additionally, (*2*) delay in initiating steroid treatment and (*3*) the presence of a higher degree of TIF on renal biopsy would predict lower steroid responsiveness.

Clarkson *et al.* (16) showed no difference in 1-year outcomes with early steroid use in biopsy-proven AIN (26 controls versus 16 steroid-treated patients). In addition to being a small study, 33% of the patients had severe TIF, which could explain the absence of observed benefit from steroids. A larger multicenter study ($N=171$) by Valluri *et al.* (17) found a trend toward complete renal recovery in the glucocorticoid group versus controls (48% versus 41%, respectively), although this was not statistically significant. A high percentage of patients in this study had an unclear duration of AKI, and only 14% had a time course of <3 weeks, which suggests that the majority may have developed significant TIF. Additionally, 35% of patients had DI-AIN attributed to PPIs. PPI-induced AIN is particularly notable for poorer prognosis due to its insidious onset and delay in diagnosis as well as baseline CKD in the elderly, who are more likely to be on chronic PPI therapy (20). Finally, glucocorticoid-treated patients had a higher severity of AKI at baseline (4.0 versus 3.2 mg/dl creatinine); therefore, similar creatinine levels in the two groups on follow-up could suggest a higher magnitude of improvement in renal function in those who received glucocorticoids.

In summary, despite a lack of data from RCTs, there is compelling evidence favoring the early use of glucocorticoid therapy in patients with DI-AIN (ideally within 7–10 days of diagnosis). This includes patients with severe AKI but without severe TIF on histopathology. Timely therapy may allow for faster and more complete renal recovery and lower risk of residual CKD. In situations in which withdrawal of the drug may be detrimental (such as lifesaving antibiotics or ICIs), treatment with glucocorticoids and drug rechallenge may be the only option (21). A short course of high-dose steroids (2–3 weeks) followed by a taper over the next 6–8 weeks is a reasonable approach. Those patients with DI-AIN who respond favorably to steroids are likely to do so by 4 weeks, and treatment beyond 6–8 weeks may increase the adverse effects with minimal additional benefit (5,10). ICIs may require longer treatment (3–6 months) and a slower taper (21). Although intravenous pulse steroids can be used for severe AKI, there does not seem to be an advantage of intravenous protocols over high-dose oral steroids (22). Finally, factors such as age, frailty, comorbidities, and overall risk versus benefit of glucocorticoid therapy in the individual patient should be considered. A prospective, open-label RCT is underway to compare prednisolone with supportive care in patients with incident biopsy-proven AIN and should provide further guidance (23).

Disclosures

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Author Contributions

N. Krishnan provided supervision; A. Donati wrote the original draft; and N. Krishnan reviewed and edited the manuscript.

References

1. Praga M, González E: Acute interstitial nephritis. *Kidney Int* 77: 956–961, 2010 https://doi.org/10.1038/ki.2010.89
2. Raghavan R, Eknoyan G: Acute interstitial nephritis - A reappraisal and update. *Clin Nephrol* 82: 149–162, 2014 https://doi.org/10.5414/CN10838
3. Baker RJ, Pusey CD: The changing profile of acute tubulointerstitial nephritis. *Nephrol Dial Transplant* 19: 8–11, 2004 https://doi.org/10.1093/ndt/gfg464
4. Perazella MA: Clinical approach to diagnosing acute and chronic tubulointerstitial disease. *Adv Chronic Kidney Dis* 24: 57–63, 2017 https://doi.org/10.1053/j.ackd.2016.08.003
5. Moledina DG, Perazella MA: Drug-induced acute interstitial nephritis. *Clin J Am Soc Nephrol* 12: 2046–2049, 2017 https://doi.org/10.2215/CJN.07630717
6. Muriithi AK, Leung N, Valeri AM, Cornell LD, Sethi S, Fidler ME, Nasr SH: Biopsy-proven acute interstitial nephritis, 1993-2011: A case series. *Am J Kidney Dis* 64: 558–566, 2014 https://doi.org/10.1053/j.ajkd.2014.04.027
7. Saran R, Robinson B, Abbott KC, Bragg-Gresham J, Chen X, Gipson D, Gu H, Hirth RA, Hutton D, Jin Y, Kapke A, Kurtz V, Li Y, McCullough K, Modi Z, Morgenstern H, Mukhopadhyay P, Pearson J, Pisoni R, Repeck K, Schaubel DE, Shamraj R, Steffick D, Turf M, Woodside KJ, Xiang J, Yin M, Zhang X, Shahinian V: US Renal Data System 2019 Annual Data Report: Epidemiology of kidney disease in the United States. National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases, Bethesda, MD, 2019. https://www.usrds.org/annual-data-report/
8. Krishnan N, Perazella MA: Drug-induced acute interstitial nephritis: Pathology, pathogenesis, and treatment. *Iran J Kidney Dis* 9: 3–13, 2015 http://www.ijkd.org/index.php/ijkd/article/view/1982/735
9. Rastegar A, Kashgarian M: The clinical spectrum of tubulointerstitial nephritis. *Kidney Int* 54: 313–327, 1998 https://doi.org/10.1046/j.1523-1755.1998.00001.x
10. González E, Gutiérrez E, Galeano C, Chevia C, de Sequera P, Bernis C, Parra EG, Delgado R, Sanz M, Ortiz M, Goicoechea M, Quereda C, Olea T, Bouarich H, Hernández Y, Segovia B, Praga M; Grupo Madrileño De Nefritis Intersticiales: Early steroid treatment improves the recovery of renal function in patients with drug-induced acute interstitial nephritis. *Kidney Int* 73: 940–946, 2008 https://doi.org/10.1038/sj.ki.5002776
11. Neilson EG: Mechanisms of disease: Fibroblasts—A new look at an old problem. *Nat Clin Pract Nephrol* 2: 101–108, 2006 https://doi.org/10.1038/ncpneph0093
12. Raza MN, Hadid M, Keen CE, Bingham C, Salmon AH: Acute tubulointerstitial nephritis, treatment with steroid and impact on renal outcomes. *Nephrology (Carlton)* 17: 748–753, 2012 https://doi.org/10.1111/j.1440-1797.2012.01648.x

13. Prendecki M, Tanna A, Salama AD, Tam FW, Cairns T, Taube D, Cook HT, Ashby D, Duncan ND, Pusey CD: Long-term outcome in biopsy-proven acute interstitial nephritis treated with steroids. *Clin Kidney J* 10: 233–239, 2017
14. Fernandez-Juarez G, Perez JV, Caravaca-Fontán F, Quintana L, Shabaka A, Rodriguez E, Gadola L, de Lorenzo A, Cobo MA, Oliet A, Sierra M, Cobelo C, Iglesias E, Blasco M, Galeano C, Cordon A, Oliva J, Praga M; Spanish Group for the Study of Glomerular Diseases (GLOSEN): Duration of treatment with corticosteroids and recovery of kidney function in acute interstitial nephritis. *Clin J Am Soc Nephrol* 13: 1851–1858, 2018 https://doi.org/10.2215/CJN.01390118
15. Huang L, Liang S, Dong J, Fan W, Zeng C, Zhang T, Cheng S, Ge Y: Prognosis of severe drug-induced acute interstitial nephritis requiring renal replacement therapy. *Ren Fail* 43: 1020–1027, 2021 https://doi.org/10.1080/0886022X.2021.1942914
16. Clarkson MR, Giblin L, O'Connell FP, O'Kelly P, Walshe JJ, Conlon P, O'Meara Y, Dormon A, Campbell E, Donohoe J: Acute interstitial nephritis: Clinical features and response to corticosteroid therapy. *Nephrol Dial Transplant* 19: 2778–2783, 2004 https://doi.org/10.1093/ndt/gfh485
17. Valluri A, Hetherington L, Mcquarrie E, Fleming S, Kipgen D, Geddes CC, Mackinnon B, Bell S: Acute tubulointerstitial nephritis in Scotland. *QJM* 108: 527–532, 2015 https://doi.org/10.1093/qjmed/hcu236
18. Guijarro C, Egido J: Transcription factor-κ B (NF-κ B) and renal disease. *Kidney Int* 59: 415–424, 2001 https://doi.org/10.1046/j.1523-1755.2001.059002415.x
19. Raghavan R, Shawar S: Mechanism of drug-induced interstitial nephritis. *Adv Chronic Kidney Dis* 24: 64–71, 2017 https://doi.org/10.1053/j.ackd.2016.11.004
20. Moledina DG, Perazella MA: PPIs and kidney disease: From AIN to CKD. *J Nephrol* 29: 611–616, 2016 https://doi.org/10.1007/s40620-016-0309-2
21. Perazella MA, Shirali AC: Immune checkpoint inhibitor nephrotoxicity: What do we know and what should we do? *Kidney Int* 97: 62–74, 2020 https://doi.org/10.1016/j.kint.2019.07.022
22. Chowdry AM, Azad H, Mir I, Najar MS, Ashraf BM, Muzafar WM, Ahmed WI: Drug-induced acute interstitial nephritis: Prospective randomized trial comparing oral steroids and high-dose intravenous pulse steroid therapy in guiding the treatment of this condition. *Saudi J Kidney Dis Transpl* 29: 598–607, 2018 https://doi.org/10.4103/1319-2442.235171
23. Mose FH, Birn H, Hoffmann-Petersen N, Bech JN: Prednisolone treatment in acute interstitial nephritis (PRAISE) - Protocol for the randomized controlled trial. *BMC Nephrol* 22: 161, 2021 https://doi.org/10.1186/s12882-021-02372-4

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